Vasculitis and arthropathy in cystic fibrosis

Margaret E Hodson MD FRCP *Department of Cystic Fibrosis, Royal Brompton & National Heart Hospital, Sydney Street, London SW3 6NP*

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Vasculitis

Vasculitis is a disorder involving venules, capillaries, arterioles and larger vessels. It can affect the skin alone or any other organ. The cellular reaction may be neutrophils, lymphocytes or granulomatous in nature. It is an unusual complication of cystic fibrosis (CF). The term vasculitis has been used to describe many clinically differing disorders, namely urticaria, allergic vasculitis, anaphylactoid purpura, drug eruptions, infection, erythema multiforme, erythema nodosa, polyarteritis nodosa, focal granulomatous lesions and systemic lupus erythematosis. It is thought to be due to inappropriate activity of the immune response causing liberation of inflammatory mediators, deposition of immune complexes and infiltration with cells. Some cases we have seen in recent years in patients with CF and reported by Finnegan *et al.*[1] are described below. The results of investigations are given in Table 1.

Case 1

A 19-year-old man (FEV_1 16% predicted, FVC 23% predicted) was admitted with a purpuric rash (Figure 1) of 4 hours duration. The rash was palpable and spread from the legs to the thighs and elbows. The symptoms subsided and he was discharged from hospital. Ten days later he was admitted severely ill with haemoptysis, recurrence of his rash affecting the whole body haematuria, proteinuria, periorbital oedema, ascites and ankle oedema. He was commenced on prednisolone but had grand mal convulsions and died. At necropsy the brain showed petechial haemorrhages, an infarct in the right occipital lobe and vasculitis affecting the adjacent vessels. The kidney showed a focal glomerular sclerosis and capsular adhesions.

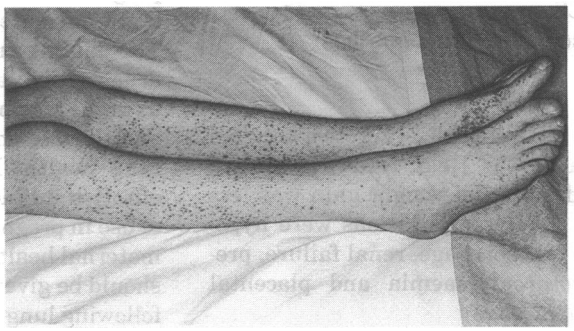

Figure 1. Typical vasculitic rash (reproduced by permission of the Quarterly Journal of Medicine[1])

Case 2

A man aged 32 years (FEV_1 80% predicted, FVC 94% predicted) was admitted with an itchy purpuric rash on his ankles and arthralgia of knees and joints. The rash was palpable and spread to his thighs, hands and forearms. The interphalangeal joints became tender. He had haematuria and proteinuria. A skin biopsy showed a mixed cellular infiltrate of the dermis, particularly associated with superficial vessels. The capillaries showed swelling and degeneration of endothelial cells and there was extravasation of red cells and disintegration of the leucocyte nuclei. Immunofluorescence for immunoglobins and C3 was

Table 1. Results of investigations[1]

Investigation (reference range and units)	*Case report*			
	1	*2*	*3*	*4*
ESR (mm/h)	1	97	30	70
Urea (normal 2.5-6.5 mmol/l)	9.3	5.9	4.8	2.7
Creatinine (normal 60-120 μmol/l)	100	90	60	35
Creatinine clearance (normal > 80 ml/min)	19	48	116	94
Urinary protein (normal < 0.2 g)	1.5	2.7	0.2	0.1
Anti-neutrophil cytoplasmic antibody	–	–	+	–
IgG (normal 6.5-16 g/l)	18.2	17.2	15.7	38.1
IgA (normal 0.4-3.2 g/l)	11.0	9.4	3.7	9.5
IgM (normal 0.5-3.52 g/l)	0.7	1.4	1.7	2.3
Immune complexes (normal < 20 μg/ml)	128	> 300	53	ND
Antinuclear factor	ND	ND	–	–
Anti DS DNA	ND	ND	–	–
HBsAg	–	–	–	–
ASO titre	–	–	–	–
Viral screen	–	–	+*	–

*CMV titre positive at 1 : 80
ND=not done

negative. A renal biopsy showed crescents in 25% of glomeruli. The arterioles showed focal endothelial swelling, and there were fine granular deposits of IgA, mainly in the capillary walls but also in the mesangium. The findings were typical of Henoch Schonlein purpura. The patient was treated with prednisolone and azathioprine, and the rash subsided.

Case 3

A 24-year-old woman (FEV_1 38% predicted, FVC 64% predicted) developed a macular rash on her lower limbs. Initially there was no systemic upset but later she developed abdominal pain and vomiting. This subsided and the rash faded. Four months later she had a pulmonary exacerbation and again the rash recurred affecting the lower limbs. It was itchy and tender to touch. Biopsy showed an acute and chronic perivascular inflammatory infiltrate consistent with vasculitis. She had no haematuria. The rash subsided with prednisolone therapy.

Case 4

A 12-year-old boy (FEV_1 62% predicted, FVC 88% predicted) had non-insulin dependent diabetes and hepatic cirrhosis. He developed a purpuric rash on the ankles, legs and hands whilst being treated for an exacerbation of pulmonary infection. His antibiotics were stopped and the rash faded. He complained of aching limbs. A skin biopsy showed a leucocytoclastic vasculitis.

Other cases

Having been made aware of this condition by these four cases, we scanned the cystic fibrosis database which records clinical details on all patients admitted since 1965. We found evidence of eight more patients who probably had vasculitis, although no biopsies were taken. Very brief clinical details are shown in Table 2.

Discussion

Three of the four cases reported in detail showed raised levels of immune complexes and raised IgG. All four had a raised IgA. Anti-neutrophil cytoplasmic antibody tests were done on 10 of the 12 cases in whom serum was available, and in four cases these were positive, compared with sera from 61 CF patients without vasculitis none of whom had a positive ANCA test. In one of these 10 patients we found that tissue from a skin biopsy stained positive for anti-staphylococcal antibody. For all patients hepatitis B surface antigen, rheumatoid factor, antinuclear factor and antistreptolysin O titre were negative.

The possible causes of vasculitis in these patients include reaction to bacterial antigens, hypergammaglobulinaemia, drugs and circulating immune complexes. We only found evidence of bacterial antigen in one skin biopsy but elevated levels of circulating immune complexes were found in several patients. All 12 patients were on multiple medications including pancreatic enzymes, vitamins, bronchodilators and antibiotics.

Table 2. Clinical course of vasculitic rash in 8 further patients with cystic fibrosis[1]

Case	Clinical course
A	Several relapses over 5 months, spontaneously clearing
B	Rash only present in final illness
C	Several relapses over 2 years. Markedly improved on steroids
D	Several relapses over 2 years. Spontaneously clearing
E	Rash only in final illness (carcinoma of ileocaecal valve)
F	Rash 1 months before death. Cleared spontaneously
G	Rash 2 months before death. Cleared spontaneously
H	Rash for 1 month. Cleared spontaneously

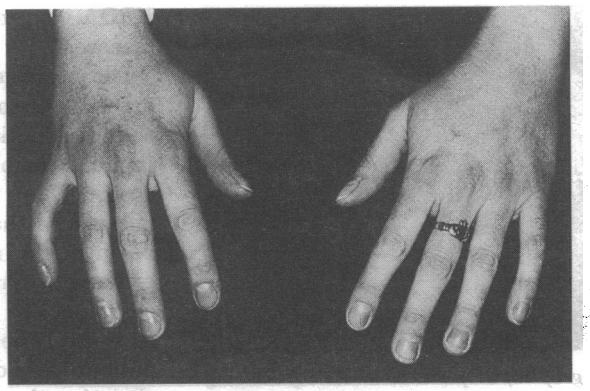

Figure 2. Acute episodic arthritis (reproduced by permission of Annals of Rheumatic Diseases[5]*)*

Systemic vasculitis has been reported in CF[1,2] and in Soter's report, necropsy examination showed necrotizing vasculitis with intraluminal thrombi affecting blood vessels in the skin, liver and gastrointestinal tract. Benign hypergammaglobulinaemic purpura of Waldenstrom has been recorded in CF without vasculitis[3]. Vasculitis has also been described in patients with non-CF bronchiectasis[4].

In conclusion, vasculitis usually confined to the skin occurs in CF, but rarely it may become systemic. In the latter case urgent treatment is required with steroids and immunosuppressive drugs. The cause is probably multifactorial including bacterial antigens, hypergammaglobulinaemia, immune complexes and drug therapy. Anti-neutrophil cytoplasmic antibody is a marker in some cases of vasculitis associated with CF.

Arthropathy

The life expectancy of patients with CF has improved much in recent years, and musculoskeletal symptoms are common particularly in older patients. In a group of 250 CF patients reported from the Royal Brompton Hospital, 29 (12%) had some kind of arthropathy[5]. There appear to be two distinct types of arthropathy, an episodic arthritis and hypertrophic pulmonary osteoarthropathy (HPOA). Episodic arthropathy can start at any age, and the patient develops widespread joint pains of sudden onset with flu-like symptoms. Pain may be very severe, and there may be associated erythema and joint swelling (Figure 2). The episode of arthropathy lasts 3-4 days, and in some patients it may be associated with erythema nodosa. Symptoms usually settle with non-steroidal anti-inflammatory drugs although occasionally prednisolone is needed. In this group of patients, rheumatoid factor and ANA were not detected. There may be a raised erythrocyte sedimentation rate (ESR) and a raised level of immune complexes.

In other patients, HPOA tends to occur at a later age of onset and present with bone pain in the wrists, knees and ankles, the lower limbs being affected more than the upper limbs. Effusions may

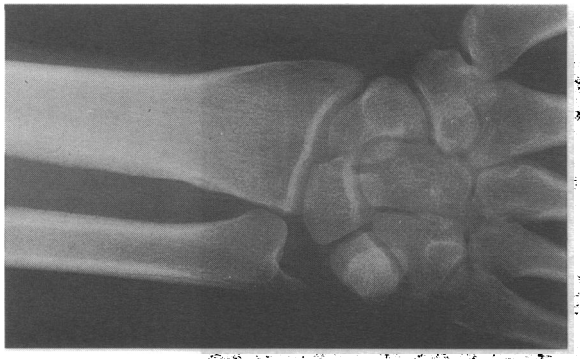

Figure 3. Wrist radiograph of CF patient with HPOA showing periosteal new bone formation at distal ends of radius and ulna (reproduced by permission of Annals of Rheumatic Diseases[5])

occur, particularly in the knees and patients may experience difficulty in walking. It appears to be less painful than the episodic arthritis. Some of these patients show a raised ESR, and raised loads of circulating immune complexes. A radiograph of the long bones usually show periostitis (Figure 3).

Occasionally, patients with CF will have myalgia of unknown cause, or other diseases such as ankylosing spondylitis or rheumatoid arthritis. Occasionally drug-related arthropathies may occur. The group of patients with CF and hypertrophic pulmonary osteoarthropathy ($n=10$) and the group of patients with episodic arthritis ($n=12$) reported from the Brompton Hospital[5] show that the mean percent predicted FEV_1 for those with HPOA was 26%, and the mean for those with episodic arthritis was 58%. This is clinically significant, and seems to indicate that the arthropathy associated with HPOA is related to more severe pulmonary disease.

The pathogenesis of both episodic arthritis and arthritis associated with HPOA is obscure. On occasions patients have raised levels of circulating immune complexes, but in the majority of cases they do not. There is no associated with HLA type and it is possible that some neurogenic mechanism may be involved in the hypertrophic pulmonary osteoarthropathy group. It has now been observed that both clubbing and periosteal reactions disappear after successful heart-lung transplantation when the patient has a denervated lung. However in the same situation there is the removal of the infected lung which is a source of bacterial antigens.

In conclusion arthropathy occurs in about 10% of adolescents and older patients with CF. There appear to be two types, an episodic arthritis and hypertrophic pulmonary osteoarthropathy. The treatment is with non-steroidal anti-inflammatory agents, and occasionally in episodic arthritis a short course of steroids is needed. Detailed aetiology remains obscure.

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